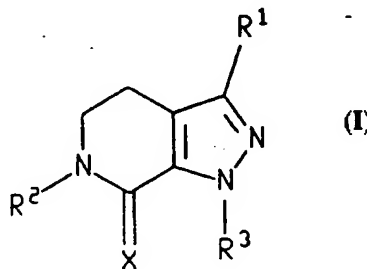




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| (54) Title: BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINES (57) Abstract Compounds of formula (I) wherein R ¹ , R ² , R ³ and X are as defined. The compounds of formula (I) and the pharmaceutically acceptable salts thereof are useful in inhibiting phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) and in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF. | | |



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BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINESBackground of the Invention

This invention relates to a series of bicyclic tetrahydro pyrazolopyridines which are selective inhibitors of phosphodiesterase (PDE) type IV or the production of tumor
10 necrosis factor (hereinafter TNF) and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases; and AIDS, septic shock and other diseases involving the production of TNF.

This invention also relates to a method of using such compounds in the
15 treatment of the above diseases in mammals, especially humans and to pharmaceutical compositions useful therefor.

Since the recognition that cyclic AMP is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic
20 intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J.A. Beavo and D. H. Reifsnyder, TiPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C.D. Nicholson, R. A. Challiss and M. Shahid, TiPS, 1991, 12, 19). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M.W. Verghese
25 et al., J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing
30 cardiovascular effects or antiplatelet effects.

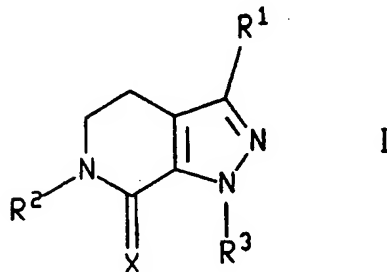
TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62, S11).

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Summary of the Invention

The present invention relates to compounds of the formula

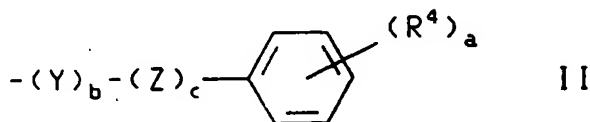
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I

- 10 and the pharmaceutically acceptable salts thereof; wherein R¹ is hydrogen, (C¹-C⁷)alkyl, (C²-C³)alkenyl, (C³-C⁵)cycloalkyl or methylene (C³-C⁵)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C¹-C²)alkyl or trifluoromethyl groups or up to three halogens; X is oxygen or two hydrogen atoms; R² and R³ are each independently selected from the group consisting of hydrogen, (C¹-C¹⁴)alkyl, (C¹-C¹⁴)alkoxy, (C²-C⁷)alkenyl, a (C⁴-C⁷)heterocyclic group containing oxygen, sulphur, SO₂, or NR⁵ wherein R⁵ is hydrogen or (C¹-C⁴)alkyl, or a group of the formula

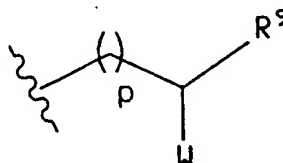
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II

- wherein a is an integer from 1 to 5; b and c is 0 or 1; R⁴ is hydrogen, hydroxy, (C¹-C⁵)alkyl, (C²-C⁵)alkenyl, (C¹-C⁵)alkoxy, (C³-C⁶)cycloalkoxy, halogen, trifluoromethyl, CO₂R⁶, CONR⁶R⁷, NR⁶R⁷, NO₂ or SO₂NR⁶R⁷ wherein R⁶ and R⁷ are each independently hydrogen or (C¹-C⁴)alkyl; wherein Z is oxygen, sulphur, SO₂ or NR⁸ wherein R⁸ is hydrogen or (C¹-C⁴)alkyl; and Y is (C¹-C⁵)alkylene or (C²-C⁶)alkenyl optionally substituted with up to two (C¹-C⁷)alkyl or (C³-C⁷)cycloalkyl groups; or a group of the formula

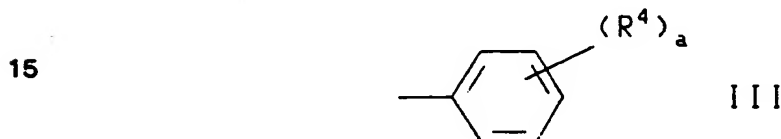
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wherein p is an integer from 1 to 3, W is oxo or hydroxy, R⁹ is (C¹-C³)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C¹-C²)alkyl, trifluoromethyl or halogen with the proviso that when R¹ is ethyl and R² is 4-methylphenyl, R³ cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R² is 4-methylphenyl and R³ is 4-fluorophenyl, R¹ cannot be phenyl, methyl or n-propyl and with the proviso that when R¹ is ethyl and R² is phenyl, R³ cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl and with the proviso that when R¹ is ethyl and R² is 4-methoxyphenyl, R³ cannot be 4-fluorophenyl.

10 In one embodiment, the invention relates to a compound of formula I wherein R¹ is (C¹-C³)alkyl and R² and R³ are each independently selected from the group consisting of (C³-C⁷)cycloalkyl, (C⁴-C⁷)heterocyclic group containing SO₂ or a group of the formula



wherein a is an integer from 1 to 5 and R⁴ is hydrogen, hydroxy, (C¹-C⁵)alkyl, (C¹-C⁵)alkoxy or halogen.

20 In another embodiment, the invention relates to a compound of formula I wherein R¹ is ethyl or isopropyl; R² is phenyl, 2-methylphenyl, 3-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl or 3-trifluoromethylphenyl and R³ is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising a pharmaceutically effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

25 The present invention further relates to a method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

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The present invention further relates to a method of treating an inflammatory condition in mammals which comprises administering to said mammal an antiinflammatory amount of a compound of the formula I and the pharmaceutically acceptable salts thereof.

5 The present invention further relates to a pharmaceutical composition for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound according to formula I and the pharmaceutically acceptable
10 salts thereof together with a pharmaceutically acceptable carrier.

This invention further relates to a method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising
15 administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

Specific preferred compounds of the invention are:

- 3-ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-
[3,4-c]pyridine;
- 20 3-ethyl-1-cyclopentyl-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-
[3,4-c]pyridine;
- 3-ethyl-1-(3,4-dichlorophenyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
pyrazolo[3,4-c]pyridine;
- 3-ethyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
25 pyrazolo[3,4-c]pyridine;
- 3-ethyl-1-(4-fluorophenyl)-6-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
pyrazolo[3,4-c]pyridine;
- 3-ethyl-1-cyclopentyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-
c]pyridine;
- 30 3-ethyl-1-cyclopentyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
pyrazolo[3,4-c]pyridine;
- 3-ethyl-1-cyclohexyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
pyrazolo[3,4-c]pyridine;

3-isopropyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

5 3-ethyl-1-cyclopentyl-6-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine:

3-ethyl-1-cyclopentyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

10 3-ethyl-1-(3-sulfolanyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-
15 pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine.

20 Detailed Description of the Invention

The term "halogen", as used herein, unless otherwise indicated, includes chloro, fluoro and bromo.

Unless indicated otherwise, the alkyl, alkoxy and alkenyl groups referred to herein may be straight chained or if comprising three or more carbons may be straight
25 chained, branched, cyclic or a combination of cyclic and branched or straight chained moieties.

The "inflammatory diseases" which can be treated according to this invention include, but are not limited to asthma, chronic obstructive pulmonary disease, bronchitis and arthritis.

30 R¹, R² and R³, as used herein, unless otherwise indicated, are as defined above with reference to formula I.

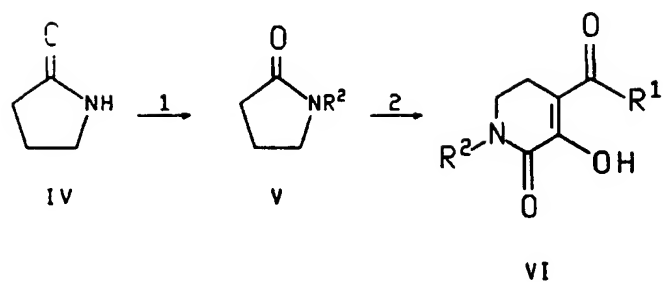
The following reaction schemes illustrate, but are not limiting to the preparation of the compounds of the present invention.

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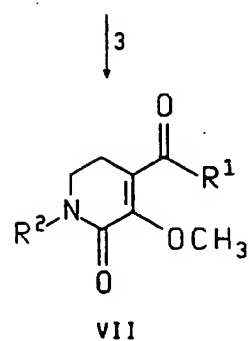
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SCHEME 1

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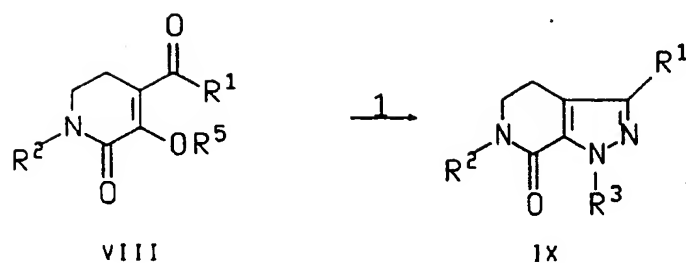
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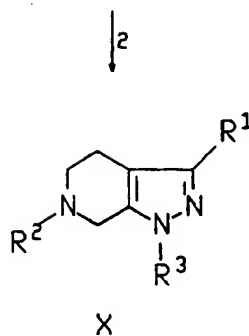
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SCHEME 2

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5 In Reaction 1 of Scheme 1, the 2-pyrrolidinone compound of formula IV is converted to the corresponding N-(aryl)-2-pyrrolidone compound V wherein "aryl" is a group of the formula II by reacting IV with an aryl halide neat in the presence of copper powder and potassium carbonate. Suitable aryl halides include 1-iodo- or 1-bromo- 4-methoxybenzene, 3-methoxybenzene, 2-methoxybenzene, 3-methylbenzene, 4-
10 methylbenzene, 2-methylbenzene, 3-trifluoromethylbenzene, 2-trifluoromethylbenzene, 3,4-dimethoxybenzene or 3-cyclopentoxy-4-methoxybenzene. The reaction temperature will generally be in the range of about 110°C to about 170°C, preferably about 150°C, for a time period of about 14 hours to about 22 hours, preferably about 18 hours, under inert reaction conditions.

15 In Reaction 2 of Scheme 1, R¹ halide is added to a suspension of magnesium in an anhydrous aprotic solvent. The reaction mixture is heated to reflux until all the magnesium is consumed and thereafter cooled to a temperature between about -15°C to about 15°C, preferably about 0°C. The N-(aryl)-2-pyrrolidone compound of formula V is then added and the reaction mixture is warmed to room temperature while being
20 stirred for a time period between about 1.5 hours to about 2.5 hours, preferably about 2 hours. Suitable alkyl halides include bromomethane, bromoethane or bromopropane. The preferred anhydrous aprotic solvent is anhydrous ether. Upon completion of the reaction, the desired intermediate may be isolated in a conventional manner, e.g., by first washing the combined organics with water and brine, then drying
25 over sodium sulfate, filtering and concentrating under reduced pressure to afford a readily-recoverable precipitate in the form of a white solid.

The above precipitate is converted to the corresponding 1,2,5,6-tetrahydropyridine compound of formula VI by dispersing the precipitate in a mixture of a non-polar aprotic solvent and base. Upon vigorous stirring, ethyl oxalyl chloride
30 is added and the reaction mixture is heated to reflux for a time period between about 1.5 hours to about 4.5 hours, preferably about 3.0 hours. The preferred non-polar aprotic solvent is benzene and the preferred base is sodium hydroxide. The solvents are removed and the resulting residue is treated with a solution of sodium alkoxide in ethanol. After heating at reflux for a time period between about 1 hour and about 3
35 hours, preferably about 1.5 hours, the mixture is concentrated under reduced pressure and acidified to pH=3 with hydrochloric acid.

In Reaction 3 of Scheme 1, the compound of formula VI is converted to the corresponding 3-methoxy-1,2,5,6-tetrahydropyridine compound VII by heating to reflux a reaction mixture of VI and 3-methyl-1-p-tolyltriazene in an aprotic solvent. The preferred aprotic solvent is 1,2-dichloroethane. The time period for the reaction is
5 between about 30 minutes to about 120 minutes, preferably about 45 minutes.

In Reaction 1 of Scheme 2, the 1,2,5,6-tetrahydropyridine compound of formula VIII, wherein R^5 is hydrogen or methyl, is converted to the corresponding 4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo[3,4-c]pyridine compound IX by reacting VIII with a hydrazine of the formula R^3HNNH_2 . Both derivatives of the compound of formula VIII,
10 3-hydroxy and 3-methoxy, may be used as starting materials under one of three different sets of reaction conditions.

Under one set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula VIII is converted to the corresponding compound of formula IX by reacting VIII with a hydrazine hydrochloride and sodium alkoxide in an anhydrous polar protic
15 solvent. The preferred sodium alkoxide is sodium methoxide and the preferred anhydrous polar protic solvent is anhydrous ethanol. The reaction mixture is heated to reflux for a time period between about 9 hours to about 15 hours, preferably about 12 hours.

Under a second set of reaction conditions, the 1,2,5,6-tetrahydro-pyridine
20 compound VIII is converted to the corresponding compound of formula IX by reacting VIII with hydrazinobenzoic acid in an anhydrous polar protic solvent, preferably ethanol. The reaction mixture is heated to reflux for a time period between about 16 hours to about 24 hours, preferably about 20 hours. The compound IX so formed may be further reacted to give the corresponding 1-(4-benzamide)-7-oxo-4,5,6,7-tetrahydro-1H-
25 pyrazolo[3,4-c]pyridine compound by reacting IX with sodium methoxide in a polar protic solvent, preferably methanol, for a time period between about 15 minutes to about 45 minutes, preferably 30 minutes. The polar protic solvent is removed under reduced pressure, the solid residue is suspended in a non-polar aprotic solvent, preferably benzene, and thereafter, the non-polar solvent is removed under reduced
30 pressure. The resulting dry solid is suspended in cold ether and treated with oxalyl chloride and N,N-dimethylformamide and allowed to stir for a time period between about 30 minutes to about 90 minutes, preferably 60 minutes. The solvent is then removed and the crude residue is dissolved in dry tetrahydrofuran. The resulting

solution is added dropwise to stirred ammonium hydroxide at a temperature between about -10°C to about 10°C, preferably 0°C.

Under a third set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula VIII is converted to the corresponding compound of formula IX
5 by reacting VIII with a hydrazine hydrochloride in a polar protic solvent, preferably methanol. The reaction mixture is heated to a temperature between about 70°C to about 110°C, preferably about 90°C, under a gentle stream of nitrogen until all of the solvent is removed. The neat mixture is then heated to a temperature between about 120°C to about 180°C, preferably about 150°C, for a time period between about 30
10 minutes to about 90 minutes, preferably 60 minutes.

The compounds so formed of formula IX may be converted to the corresponding 6-R²-4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo [3,4-c]pyridine compound, wherein R² is other than the group of formula II, by reacting a solution of IX in a polar aprotic solvent, preferably acetonitrile, with a solution of ammonium cerium (IV) nitrate
15 in water at a temperature between about -15°C to about 15°C, preferably about 0°C, for a time period between about 20 minutes to about 50 minutes, preferably about 35 minutes. Upon completion of the reaction, the mixture is diluted with water and extracted with ethyl acetate. The combined organics are then washed with saturated sodium bicarbonate followed by sodium sulfite. The compound so formed in a polar
20 aprotic solvent, preferably tetrahydrofuran, is treated with sodium hydride, heated to reflux and stirred for a time period between about 30 minutes to about 60 minutes, preferably 45 minutes. The reaction mixture is cooled to a temperature between about 20°C to about 30°C, preferably about 25°C, and an alkyl halide of formula R² halide, wherein R² is as defined with reference to formula I other than a group of formula II, is
25 added. The reaction mixture is stirred and heated to reflux for a time period between about 12 hours to about 20 hours, preferably 16 hours:

In Reaction 2 of Scheme 2, the 2-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine compound IX is converted to the corresponding compound of formula X by reacting IX with a reducing agent, preferably lithium aluminum hydride, in a non-polar
30 aprotic solvent, preferably ether. The reaction is stirred for a time period between about 12 hours to about 20 hours, preferably 16 hours. Water and base, preferably sodium hydroxide, is then added and the reaction mixture is stirred for a time period between

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about 1.5 hours to about 2.5 hours, preferably 2 hours, and filtered. The filtrate is concentrated to a white solid.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase IV (PDE_4) and, consequently, demonstrate their effectiveness for treating inflammatory diseases is shown by the following in vitro assay.

BIOLOGICAL ASSAY

(Human lung PDE_{IV})

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 μ m filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity, determined by [3 H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μ M compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

- i) 25 μ l compound or DMSO (1%, for control and blank)
- ii) 25 μ l pH 7.5 Tris buffer
- iii) [3 H]cAMP (1 μ M)
- iv) 25 μ l PDE_{IV} enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water

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bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. $[^3\text{H}]$ cAMP is washed with 2 x 6 ml washing buffer, and $[^3\text{H}]$ 5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for $[^3\text{H}]$.

$$\% \text{ inhibition} = 1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of $[^3\text{H}]$ cAMP to $[^3\text{H}]$ 5'AMP.

(TNF)

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Peripheral blood (100 mls) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by Ficoll/Hypaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1×10^6 cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/step and nystatin). Monocytes are plated as 1×10^6 cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10 μ l) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10 μ l) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C . At the end of the incubation period TNF was analyzed by a sandwich ELISA (R&D Quantikine Kit). IC_{50} determinations are made for each compound based on linear regression analysis.

Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO_3 , H_2SO_4 , H_3PO_4 , $\text{CH}_3\text{SO}_3\text{H}$, $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$, $\text{CH}_3\text{CO}_2\text{H}$, gluconic acid, tartaric acid, maleic acid and succinic acid. Pharmaceutically-acceptable cationic salts of the compounds of this

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invention of formula I wherein R^4 is CO_2R^6 and R^6 is hydrogen include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

5 For administration to humans in the curative or prophylactic treatment of inflammatory diseases, oral dosages of the compounds of formula I and the pharmaceutically acceptable salts thereof (hereinafter also referred to as the active compounds of the present invention) are generally in the range of from 0.1-100 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual
10 tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be
15 most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For administration to humans for the inhibition of TNF, a variety of conventional
20 routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration
25 will, in any event, determine the appropriate dose for the individual subject.

For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be
30 administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovals either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously.

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For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic.

Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula I and the pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable diluent or carrier.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

Example 1

3-Ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A mixture of 3-hydroxy-2-oxo-1-phenyl-4-propionyl-1,2,5,6-tetrahydro-pyridine (1.0 g, 4.1 mmole), 4-methoxyphenylhydrazine hydrochloride (0.8 g, 4.6 mmole) and sodium methoxide (0.11 grams, 2 mmole) in 35 ml anhydrous ethanol (distilled from Mg) was heated at reflux. After 12 hours, the solvent was removed by rotary evaporation under reduced pressure, and the crude residue was chromatographed on a 4x20 cm silica column using 1:1 ether/hexane as eluent to give 345 mg of the title compound as a red oil that crystallized upon standing at room temperature. The desired 1-(4-methoxyphenyl) regioisomer is less polar than the 2-(4-methoxyphenyl) byproduct.

M.P. 43-45°C, IR (chloroform) lactam C=O, 1665 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 4.10 (t, J = 6.6 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.22-7.39 (m, 5H), 7.45 (d, J = 9.0 Hz, 2H); Anal. calcd. for C₂₁H₂₁N₃O₂: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.48; H, 6.08; N, 11.66; MS m/z (M⁺) 347.

Examples 2-15

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 1, affords the following compounds.

| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found) %C, %H, %N |
|------|----------------|----------------|----------------|---------|---|--|
| 2 | ethyl | phenyl | methyl | 80-83 | 70.56, 6.71, 16.46 | 70.61, 6.77, 15.51 |
| 3 | ethyl | phenyl | tert-butyl | 120-121 | 72.70, 7.79, 14.13 | 72.50, 7.96, 14.16 |

| | | | | | | | |
|----|----|--------|------------------|---------------------|----------------------|----------------------------|---------------------------------|
| 5 | 4 | ethyl | 4-methoxy phenyl | 4-methoxy phenyl | 42-45 | 70.01, 6.14, 11.13 | 70.05, 6.07, 11.00 |
| | 5 | ethyl | 4-fluoro phenyl | tert-butyl | 92-94 | (M ⁺) 315.1747 | HRMS (M ⁺) 315.1741 |
| | 6 | ethyl | phenyl | 3,4-dichloro-phenyl | (oil) | [M ⁺] 386.26 | MS m/z [M ⁺] 386 |
| | 7 | ethyl | 4-fluoro phenyl | 4-methoxy phenyl | 129-130 ^a | 69.03, 5.52, 11.50 | 68.75, 5.37, 11.43 |
| | 8 | methyl | phenyl | 4-fluoro phenyl | 139-140 ^b | [M ⁺] 321.3 | MS m/z [M ⁺] 322 |
| 10 | 9 | ethyl | phenyl | cyclopentyl | 73-75 | (M ⁺) 309.1841 | HRMS (M ⁺) 309.1823 |
| | 10 | methyl | phenyl | 4-methoxy phenyl | 167-168 | (M ⁺) 333.1477 | HRMS (M ⁺) 333.1477 |
| | 11 | ethyl | phenyl | 5-phenyl pentyl | (oil) | (M ⁺) 388.2389 | HRMS (M ⁺) 388.2395 |
| | 12 | methyl | 4-methoxy phenyl | 4-fluoro phenyl | 140-142 ^b | 68.36, 5.16, 11.96 | 67.92, 5.03, 11.72 |
| | 13 | methyl | 4-methoxy phenyl | 3-fluoro phenyl | 133-138 | 68.36, 5.16, 11.96 | 68.04, 5.04, 11.75 |
| | 14 | ethyl | 4-methoxy phenyl | 3,4-dichloro-phenyl | 50-60 | 60.59, 4.60, 10.09 | 60.34, 4.56, 9.86 |
| | 15 | ethyl | 3-methoxy phenyl | methyl | (oil) | [M ⁺] 285.35 | MS m/z [M ⁺] 286 |

Recrystallizing solvents: ^aisopropyl ether. ^b5% Ethyl acetate in petroleum ether.

15

Example 16

3-Ethyl-1-(4-phenylcarboxylic acid)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A mixture of 3-hydroxy-2-oxo-1-phenyl-4-propionyl-1,2,5,6-tetrahydro-pyridine (1.0 grams, 4.08 mmole), 4-hydrazinobenzoic acid (0.68 grams, 4.49 mmole) and 30 ml of anhydrous ethanol was heated at reflux. After 20 hours, the mixture was concentrated by rotary evaporation under reduced pressure, and the solid residue was suspended in a mixture of ethyl acetate (500 ml) and pH 4 buffer (200 ml). The organic layer was separated (leaving behind most of the 2-(4-phenylcarboxylic acid) byproduct), washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure.

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Recrystallization from methanol gives 0.64 grams of the title compound as an orange solid. M.P. 261-263°C, ¹H NMR (300 MHz, DMSO-d₆) δ 1.23 (t, J = 7.6 Hz, 3H), 2.68 (q, J = 7.6 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H), 7.20-7.41 (m, 5H), 7.65 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 13.05 (s, 1H); MS m/z (M⁺) 362.

5

Example 171-(4-Benzamide)-3-ethyl-6-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

To a stirred solution of sodium methoxide in methanol (prepared from 6.6 mg Na) is added 3-ethyl-6-(4-methoxyphenyl)-1-(4-phenylcarboxylic acid)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (96 mg, 0.25 mmole). After 30 minutes, methanol was removed under reduced pressure, the solid residue was suspended in benzene, and the benzene was removed under reduced pressure. The resulting dry solid was suspended in cold ether (ice-bath) and treated with oxalyl chloride (31 μl, 0.35 mmole) and anhydrous N,N-dimethylformamide (1 drop). After stirring for 1 hour the volatiles are removed under reduced pressure, and the crude residue was dissolved in dry tetrahydrofuran. The resulting solution was added dropwise to briskly stirred ammonium hydroxide at 0°C. After warming to ambient temperature over 2 hours the reaction mixture was concentrated under reduced pressure until a yellow solid begins to precipitate. At this time the mixture was diluted with water to approximately 100 ml and filtered, and the precipitate was washed with water to give 81 mg of the title compound. Decomposition point 243-245°C; ¹H NMR (DMSO-d₆) 1.24 (t, J = 7.6 Hz, 3H), 2.68 (q, J = 7.6 Hz, 2H), 2.93 (t, J = 6.5 Hz, 2H), 3.75 (s, 3H), 3.99 (t, J = 6.5 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.43 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 8.04 (s, 1H); Anal. calcd. for C₂₂H₂₂N₄O₃: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.19; H, 5.31; N, 13.55. HRMS calcd. for C₂₂H₂₂N₄O₃ [M⁺] 391.1770. Found 391.1781.

The starting 3-ethyl-6-(4-methoxyphenyl)-1-(4-phenylcarboxylic acid)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-c] pyridine was prepared using the appropriate reagents according to the procedure of example 16.

30

Example 181-(3,4-dichlorophenyl)-3-ethyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A stirred mixture of 3-methoxy-1-(3-methoxyphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydro-pyridine (0.49 grams, 1.7 mmole), 3,4-dichlorophenylhydrazine hydrochloride (0.40 grams, 1.87 mmole) and sodium methoxide (46 mg, 0.85 mmole) in anhydrous ethanol was heated to reflux. After 16 hours, the mixture was concentrated under reduced pressure and chromatographed on a silica gel column using 1:4 ethyl acetate/hexane as eluent to give a white solid. Recrystallization from ether gave 0.46 grams of white needles. M.P. 97-99°C, ¹H NMR (250 MHz, CDCl₃) 1.31 (t, J = 7.5 Hz, 3H), 2.73 (q, J = 7.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 4.09 (t, J = 6.6 Hz, 2H), 6.78-6.91 (m, 3H), 7.29-7.49 (m, 3H), 7.73 (d, J = 1.8 Hz, 1H); MS m/z [M⁺] 416.

Examples 19-42

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-methoxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 18, affords the following compounds.

| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found), %C, %H, %N |
|------|----------------|---------------------|---------------------|----------------------|---|---|
| 19 | methyl | 4-methoxy phenyl | 3,4-dichloro-phenyl | 143-144 ^a | 59.71, 4.26, 10.45 | 56.13, 4.02, 9.65 |
| 20 | ethyl | 3-methoxy phenyl | cyclopentyl | 64-65 | [M ⁺] 340.2025 | HRMS [M ⁺] 340.2046 |
| 21 | ethyl | 4-methoxy phenyl | cyclopentyl | 96-98 | 70.77, 7.42, 12.38 | 70.44, 7.68, 11.69 |
| 22 | methyl | 4-methoxy phenyl | cyclopentyl | 121-122 | 70.13, 7.12, 12.91 | 69.48, 7.10, 12.70 |
| 23 | iso-propyl | phenyl | 3,4-dichloro phenyl | oil | [M ⁺] 400.0983 | HRMS [M ⁺] 400.0966 |
| 24 | ethyl | 3,4-dimethoxyphenyl | cyclopentyl | 107-108 | [M ⁺] 369.46 | MS m/z [M ⁺] 369 |
| 25 | ethyl | 3,4-dimethoxyphenyl | 3,4-dichloro-phenyl | 190-191 ^b | 59.20, 4.74, 9.41 | 59.41, 4.46, 9.71 |

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| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found) %C, %H, %N | |
|------|----------------|-------------------------------|-------------------------------|----------------------|---|--|------------------------------|
| 26 | iso-propyl | 4-methoxy phenyl | 3,4-dichloro phenyl | 145-147 ^c | 61.40, 4.92, 9.76 | 61.29, 4.81, 9.53 | |
| 27 | propyl | 4-methoxy phenyl | cyclopentyl | 102-103 ^c | 71.36, 7.70, 11.89 | 70.98, 7.66, 11.73 | |
| 28 | iso-propyl | 3-methoxy phenyl | 3,4-dichloro-phenyl | 126-127 ^d | 61.40, 4.92, 9.76 | 61.55, 5.10, 9.97 | |
| 29 | ethyl | 4-methoxy-3-cyclopentoxypenyl | 3,4-dichloro-phenyl | 54-56 | 62.40, 5.44, 8.40 | 62.15, 5.50, 7.97 | |
| 5 | 30 | ethyl | 4-methoxy-3-cyclopentoxypenyl | 88-89 | [M ⁺] 423.55 | MS m/z [M ⁺] 423 | |
| | 31 | ethyl | 3-methoxy phenyl | 4-fluorophenyl | 139-140 ^e | 69.03, 5.79, 11.50 | 69.05, 5.42, 11.57 |
| | 32 | ethyl | 2-methoxy phenyl | cyclopentyl | 119-120 | 70.77, 7.42, 12.38 | 70.63, 7.16, 12.01 |
| | 33 | ethyl | 2-methoxy phenyl | 4-fluorophenyl | 103-104 ^f | [M ⁺] 365.41 | MS m/z [M ⁺] 366 |
| | 34 | ethyl | 3-methyl phenyl | cyclopentyl | oil | 74.27, 7.79, 12.99 | 74.54, 7.89, 12.63 |
| 10 | 35 | ethyl | 3-methyl phenyl | 4-fluorophenyl | oil | 72.19, 5.77, 12.02 | 72.06, 5.55, 11.52 |
| | 36 | ethyl | 3-trifluoromethylphenyl | cyclopentyl | oil | 63.65, 5.87, 11.13 | 63.95, 5.73, 10.97 |
| | 37 | ethyl | 3-trifluoromethylphenyl | 4-fluorophenyl | 139-140 ^f | 62.53, 4.25, 10.42 | 62.60, 4.08, 10.41 |
| | 38 | ethyl | 4-methylphenyl | cyclopentyl | 93-94 | 74.27, 7.79, 12.99 | 74.10, 7.52, 12.59 |
| | 39 | ethyl | 2-methylphenyl | 4-fluorophenyl | 141-142 ^b | 72.19, 5.77, 12.03 | 72.36, 5.52, 12.09 |
| 15 | 40 | ethyl | 2-methylphenyl | cyclopentyl | 130-131 | MW 323.44 | MS m/z 323 |

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| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found) %C, %H, %N |
|------|----------------|---------------------------|-----------------|---------|---|--|
| 41 | ethyl | 2-trifluoro-methyl-phenyl | 4-fluoro-phenyl | 48-50 | MW 403.38 | MS m/z 404 |
| 42 | ethyl | 3-methyl-phenyl | 3-sulfo-lanyl | oil | MW 373.47 | MS m/z 374 |

Recrystallizing solvents: ^a 5% Ethyl acetate/petroleum ether. ^b Isopropyl ether.

5 ^c Ethyl acetate/hexane. ^d Ethyl ether. ^e 5% Ethyl acetate/pentane. ^f Pentane.

Example 43

1-Cyclohexyl-3-ethyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 3-methoxy-1-(3-methoxyphenyl)-2-oxo-4-propionyl-1,2,5,6-pyridine
 10 (0.80 grams, 2.8 mmole) and cyclohexylhydrazine hydrochloride (0.54 grams, 3.6 mmole) in methanol (15 ml) was warmed to 90°C under a gentle stream of nitrogen until all of the solvent was removed. The neat mixture was then heated to approximately 150°C under nitrogen for 1 hour. After cooling to room temperature, the mixture was dissolved in ether and washed with 1N hydrochloric acid followed by brine,
 15 dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel using 1:1 ethyl acetate/hexane as eluent gives 0.47 grams of the title compound as a yellow oil. ¹H NMR (250 MHz, CDCl₃) 1.20-1.52 (m, 6H, including t at 1.23, J = 7.6 Hz, 3H), 1.64-1.74 (m, 1H), 1.80-2.06 (m, 6H), 2.67 (q, J = 7.6 Hz, 2H), 2.87 (t, J = 6.7 Hz, 2H), 3.82 (s, 3H), 3.97 (t, J = 6.7 Hz, 2H), 5.13 (tt, J = 4.3 and 11.3 Hz, 1H), 6.79-6.93 (m, 3H), 7.31 (t, J = 8.1 Hz, 1H); HRMS calculated for C₂₁H₂₇N₃O₂[M⁺]: 353.2103. Found: 353.2094.

Examples 44-57

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-methoxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of
 25 Example 43, affords the following compounds.

| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found) %C, %H, %N |
|------|----------------|------------------|----------------|----------------------|---|--|
| 44 | iso-propyl | 4-methoxy-phenyl | cyclo-pentyl | 102-103 ^a | [M ⁺] 354 | MS [M ⁺] 354 |

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| Ex. # | R ¹ | R ² | R ³ | M.p. °C | Mass Spectra or Analysis (calcd.) %C, %H, %N | Mass Spectra or Analysis (found) %C, %H, %N | |
|-------|----------------|---------------------------|---------------------------|----------------------|---|--|--------------------|
| 45 | iso-propyl | 3-methoxy phenyl | cyclo-pentyl | 99-100 ^b | 71.36, 7.70, 11.89 | 71.10, 7.56, 11.73 | |
| 46 | ethyl | 3-methoxy phenyl | cyclobutyl | 73-74 ^b | 70.13, 7.12, 12.91 | 70.10, 7.22, 12.93 | |
| 47 | ethyl | phenyl | methylene cyclo-propyl | 60-62 ^c | 73.19, 7.17, 14.23 | 73.34, 7.08, 13.95 | |
| 48 | ethyl | 3-methoxy phenyl | methylene cyclo-propyl | oil | [M ⁺] 326 | MS [M ⁺] 326 | |
| 5 | 49 | ethyl | 4-methoxy-phenyl | phenyl | 156-157 ^b | 72.60, 6.09, 12.10 | 72.35, 5.91, 12.02 |
| 50 | ethyl | 3-methoxy-phenyl | 3-sulfo-lanyl | oil | 58.59, 5.95, 10.79 | 58.46, 6.03, 9.82 | |
| 51 | ethyl | 3-methoxy-phenyl | 4-trifluoro-methyl-phenyl | 124-125 ^d | 63.61, 4.85, 10.12 | 63.40, 4.51, 10.09 | |
| 52 | ethyl | 3-methyl-phenyl | cyclobutyl | oil | 73.75, 7.49, 13.58 | 73.22, 7.56, 13.03 | |
| 53 | ethyl | 3-trifluoro-methyl-phenyl | 3-sulfo-lanyl | oil | MW 427.44 | MS m/z 428 | |
| 10 | 54 | ethyl | 3-trifluoro-methyl-phenyl | cyclobutyl | oil | 62.80, 5.55, 11.56 | 63.01, 5.54, 11.19 |
| 55 | ethyl | phenyl | 2-indanyl | 155-156 ^e | 77.28, 6.49, 11.76 | 77.35, 6.48, 11.08 | |
| 56 | ethyl | 2-methyl-phenyl | cyclobutyl | 100-102 | MW 309.41 | MS m/z 310 | |
| 57 | ethyl | 3-methoxy-phenyl | 2-indanyl | 60-62 ^f | MW 387.48 | MS m/z 388, 389, 390 | |

15 Recrystallization solvents: ^aEthyl acetate/pentane. ^bEthyl ether/pentane.

^cIsopropyl ether/pentane. ^dEthyl/acetate/petroleum ether. ^eEthyl acetate. ^fEthyl acetate/hexane.

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Example 583-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

To a stirred solution of 3-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.3 grams, 0.82 mmole) in 50 ml ether was added lithium aluminum hydride (33 mg, 0.86 mmole). After stirring for 16 hours water (0.5 ml) was added followed by 3N sodium hydroxide (1 ml). After stirring for 2 hours the white precipitate was filtered through celite and the filtrate is concentrated under reduced pressure. Chromatography on a silica gel column using 1:3 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a pale yellow paste. ¹H NMR (250 MHz, CDCl₃) 1.28 (t, J = 7.6 Hz, 3H), 2.66 (q, J = 7.6 Hz, 2H), 2.71 (t, J = 5.7 Hz, 2H), 3.49 (t, J = 5.7 Hz, 2H), 3.84 (s, 3H), 4.23 (s, 2H), 6.84-6.99 (m, 6H), 7.36 (d, J = 9.0 Hz, 2H); MS m/z [M⁺] 352.

Examples 59-63

Reaction of the appropriate 7-oxo-2,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with lithium aluminum hydride, analogous to the procedure of Example 58, affords the following compounds.

| Ex.# | R ¹ | R ² | R ³ | M.p. °C | Mol. Weight | Mass Spectra [M ⁺] (found) |
|------|----------------|---------------------------------|---------------------|---------|-------------|--|
| 59 | ethyl | 4-methoxy-3-cyclopentoxo phenyl | cyclopentyl | oil | 409.57 | 409 |
| 60 | ethyl | phenyl | 3,4-dichloro-phenyl | oil | 372.30 | 371.373 |
| 61 | ethyl | phenyl | cyclopentyl | oil | 295.43 | 296 |
| 62 | ethyl | 3-methoxy phenyl | cyclobutyl | oil | 311.43 | 312 |
| 63 | ethyl | 3-methoxy phenyl | cyclohexyl | oil | 339.48 | 340 |

Example 641-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A stirred solution of 1-cyclopentyl-3-ethyl-6-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (2.58 grams, 7.60 mmoles) in acetonitrile (90 ml) at 0°C is treated with a solution of ceric ammonium nitrate (12.5 grams, 22.8 mmoles)

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in water (110 ml). After stirring for 35 minutes the mixture is diluted with water (550 ml) and extracted with ethyl acetate (100 ml x 4). The combined organics are washed with 50% saturated sodium bicarbonate (250 ml) followed by 10% sodium sulfite until the aqueous wash becomes pale yellow. The organic layer is then washed further with 5 saturated bicarbonate and brine, and treated with decolorizing charcoal. After stirring for 30 minutes the mixture is dried over sodium sulfate, filtered through celite and concentrated under reduced pressure. The brown residue is recrystallized from ether to give .814 grams of a tan solid. M.P. 143-145°C; MS (M/Z) 234; ¹H NMR (250 MHz, CDCl₃) 1.21 (t, J = 7.6 Hz, 3H), 1.62-2.13 (m, 8H), 2.62 (q, J = 7.6 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 3.51 (dt, J = 2.7 and 6.8 Hz, 2H), 5.47 (s, 1H), 5.61 (pentet, J = 7.7 Hz, 1H).

Example 65

1-cyclopentyl-3-ethyl-6-cyclopropylmethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

15 A solution of 1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.21 grams, 0.92 mmoles) in THF (5 ml) is treated with 60% sodium hydride in mineral oil (40 mg, 1.01 mmoles). After stirring at reflux over 45 minutes the reaction mixture is cooled to 25°C and (bromomethyl) cyclopropane (0.31 grams, 2.29 mmoles) is added. The mixture is stirred at reflux for 16 hours and then cooled to 25°C before 20 concentrating under reduced pressure. Chromatography on silica gel eluting with 1:1 ethyl acetate/hexane gives 0.19 grams of the title compound as a colorless oil. MS m/z [M⁺] 288; ¹H NMR (300 MHz, CDCl₃) 0.26-0.31 (m, 2H), 0.50-0.56 (m, 2H), 0.85-1.06 (m, 1H), 1.20 (t, J = 7.6 Hz, 3H), 1.62-2.08 (m, 8H), 2.61 (q, J = 7.6 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 3.39 (d, J = 6.9 Hz, 2H), 3.63 (t, J = 6.8 Hz, 2H), 5.67 (pentet, J = 25 7.8 Hz, 1H).

Preparation 1

4-Isobutyryl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine

A stirred solution of freshly distilled diisopropylamine (0.16 ml, 2.21 mmole) in anhydrous tetrahydrofuran (4 ml) was cooled to 0°C and treated with 2.5 M n-butyl lithium (0.85 ml, 2.11 mmole). After 15 minutes the mixture was cooled to -78°C and 30 a pre-cooled solution of 4-propionyl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine (0.52 grams, 2.0 mmole) in tetrahydrofuran (4 ml) was added dropwise via cannula. After approximately 20 minutes methyl iodide (0.20 ml, 3.0

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mmole) was added to the bright orange-red solution and the mixture was allowed to come to room temperature over 2.5 hours. The reaction mixture is poured into saturated aqueous ammonium chloride and the organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure.

- 5 Chromatography on a silica gel column using 1:4 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a yellow oil and 0.1 grams of recovered starting material. ¹H NMR (250 MHz, CDCl₃) 1.15 (d, 6H), 2.72 (t, 2H), 3.47 (heptet, 1H), 3.82 (t, 2H), 3.97 (s, 3H), 7.21-7.45 (m, 5H); MS m/z [M⁺] 274.

Preparations 2-3

- 10 Reaction of the appropriate 3-methoxy-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine with lithium diisopropylamine and methyl iodide, analogous to the procedure of preparation 1, affords the following compounds of formula VII.

| Prep# | R ² | m.p. °C | M.W. | Mass Spectra [M ⁺] |
|-------|-----------------|---------|--------|--------------------------------|
| 2 | 4-methoxyphenyl | oil | 303.36 | 304 |
| 15 3 | 3-methoxyphenyl | oil | 303.36 | 304 |

Preparation 4

3-Methoxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

- 20 A solution of 3-hydroxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine (5.9 grams, 23 mmole) and 3-methyl-1-p-tolyltriazine (5.1 grams, 34 mmole) in 1,2-dichloroethane was heated to reflux for 45 minutes. The mixture was allowed to cool to room temperature and was poured into water and acidified with 6N hydrochloric acid. The aqueous layer was extracted 3 times with methylene chloride,
- 25 and the combined organics are washed with 1N hydrochloric acid followed by water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting quantitative brown oil was clean by thin layer chromatography and ¹H NMR and was used without purification. ¹H NMR (300 MHz, CDCl₃) 1.12 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 2.71 (t, J = 6.7 Hz, 2H), 2.93 (q, J = 7.2 Hz, 2H), 3.77 (t, J =
- 30 6.8 Hz, 2H), 3.94 (s, 3H), 7.20 (s, 4H); MS [M⁺] 273.

Preparations 5-14

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Reaction of the appropriate 3-hydroxy-1-aryl-2-oxo-4-alkanoyl-1,2,5,6-tetrahydropyridine with 3-methyl-1-p-tolyltriazine, analogous to the procedure of Preparation 4, affords the following compounds of formula VI.

| Prep# | R ¹ | R ² | m.p. °C | M.W. | Mass Spectra [M ⁺] |
|-------|----------------|--------------------------------|---------|--------|--------------------------------|
| 5 | ethyl | phenyl | oil | 259.31 | 260 |
| 6 | methyl | 4-methoxyphenyl | oil | 275.30 | 275 |
| 7 | ethyl | 4-methoxyphenyl | 81-82 | 289.33 | 289 |
| 8 | n-propyl | 4-methoxyphenyl | oil | 303.36 | 303 |
| 9 | ethyl | 3-methoxyphenyl | 59-60 | 289.33 | 289, 290 |
| 10 | ethyl | 2-methoxyphenyl | oil | 289.33 | 289 |
| 11 | ethyl | 3,4-dimethoxyphenyl | oil | 319.26 | 319 |
| 12 | ethyl | 3-cyclopentoxo-4-methoxyphenyl | oil | 373.45 | 373 |
| 13 | ethyl | 3-methylphenyl | oil | 273.33 | 273 |
| 14 | ethyl | 3-trifluoromethylphenyl | oil | 327.30 | 327 |

Preparation 15

3-Hydroxy-1-(3-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

To a stirred suspension of magnesium turnings (1.9 grams, 79 mmole) in 30 ml of anhydrous ether was added dropwise bromoethane (5.9 ml, 79 mmole). A mild reflux was initiated after approximately 1 ml was added. After all of the magnesium was consumed, the reaction mixture was cooled to 0°C and N-(3-methylphenyl)-2-pyrrolidone (8.7 grams, 50 mmole) was added at once. After warming to room temperature and stirring for 2 hours the reaction mixture was poured over ice and extracted with ethyl acetate. The combined organics are washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 8.8 grams of a white solid.

The above solid is dispersed in a mixture of 40 ml benzene and 86 ml 1N sodium hydroxide, and with vigorous mechanical stirring ethyl oxalyl chloride (7.2 ml, 64 mmole) was added. After stirring at reflux over 1.5 hours the layers are separated and the aqueous layer was extracted with ethyl acetate. The combined organics are

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washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give an amber oil. GCMS [M^+] 305.

The above intermediate was dissolved in 20 ml anhydrous ethanol and treated with a solution of sodium methoxide in methanol (prepared from the careful addition of sodium (1.0 grams) to 10 ml anhydrous methanol). After being stirred at reflux over 1.5 hours, the mixture was concentrated under reduced pressure and 100 ml of water was added. The mixture was acidified to pH 3 with 6N hydrochloric acid and the dull yellow precipitate was filtered and washed with water. Recrystallization from 75 ml isopropyl ether affords 6.8 grams of pale yellow crystals. M.P. 115-116°; 1H NMR (300 MHz, $CDCl_3$) 1.16 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 2.74-2.82 (m, 4H), 3.85 (t, J = 6.8 Hz, 2H), 7.08-7.14 (m, 3H), 7.30 (t, J = 7.7 Hz, 1H); MS m/z [M^+] 259.

Preparations 16-29

Reaction of the appropriate 2-pyrrolidinone with the requisite alkylmagnesium bromide, followed by treatment with ethyl oxalyl chloride and base, analogous to that reported in Preparation 15, affords the following compounds of formula VI.

| Prep# | R ¹ | R ² | m.p. °C | M.W. | Mass Spectra [M^+] |
|-------|----------------|-------------------------|---------|--------|------------------------|
| 16 | methyl | phenyl | oil | 231.25 | 231 |
| 17 | ethyl | phenyl | 140-142 | 245.28 | 245 |
| 18 | ethyl | 4-fluorophenyl | 133-135 | 263.27 | 263 |
| 19 | methyl | 4-methoxyphenyl | oil | 261.28 | 262 |
| 20 | ethyl | 4-methoxyphenyl | 121-122 | 275.30 | 276 |
| 21 | n-propyl | 4-methoxyphenyl | 125-126 | 289.33 | 289 |
| 22 | ethyl | 3-methoxyphenyl | 129-130 | 275.30 | 275 |
| 23 | ethyl | 2-methoxyphenyl | 119-120 | 275.30 | 275 |
| 24 | ethyl | 4-methylphenyl | 110-112 | 259.30 | 260 |
| 25 | ethyl | 2-methylphenyl | oil | 259.30 | 259 |
| 26 | ethyl | 3-trifluoromethylphenyl | 117-118 | 313.28 | 313 |
| 27 | ethyl | 2-trifluoromethylphenyl | oil | 313.28 | 313 |
| 28 | ethyl | 3,4-dimethoxyphenyl | 179-180 | 305.33 | 306 |

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| Prep# | R ¹ | R ² | m.p. °C | M.W. | Mass Spectra [M ⁺] |
|-------|----------------|--------------------------------|---------|--------|--------------------------------|
| 29 | ethyl | 3-cyclopentoxy-4-methoxyphenyl | 133-134 | 359.42 | 360 |

Preparation 30

5

N-(2-Methoxyphenyl)-2-pyrrolidone

A mixture of 2-pyrrolidone (15.0 grams, 176 mmole), 2-iodoanisole (7.6 ml, 59 mmole), copper powder (7.5 grams, 117 mmole) and potassium carbonate (8.1 grams, 59 mmole) are stirred under nitrogen at 150°C. After 18 hours, the reaction mixture was filtered through a 6x15 cm pad of silica gel eluting with 1:1 ethyl acetate/hexane to give a pale yellow oil. The unreacted reagents are removed by vacuum distillation (0.6 mm, 80-100°C) leaving 9.2 grams of the title compound as a honey-like oil. ¹H NMR (300 MHz, CDCl₃) 2.20 (pentet, 2H), 2.55 (t, 2H), 3.75 (t, 2H), 3.82 (s, 3H), 6.93-7.02 (m, 2H), 7.25-7.30 (m, 2H); MS m/z [M⁺] 191.

Preparations 31-39

15

Reactions of the appropriate iodo- or bromobenzene with 2-pyrrolidinone, analogous to that reported in Preparation 30, affords the following compounds of formula V.

20

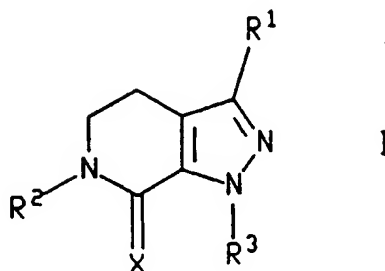
25

| Prep# | R | M.W. | Mass Spectra [M ⁺] |
|-------|--------------------------------|--------|--------------------------------|
| 31 | 4-methoxyphenyl | 191.22 | 191 |
| 32 | 3-methoxyphenyl | 191.22 | 191 |
| 33 | 3-methylphenyl | 175.23 | 175 |
| 34 | 4-methylphenyl | 175.23 | 175 |
| 35 | 2-methylphenyl | 175.23 | 175 |
| 36 | 3-trifluoromethylphenyl | 229.20 | 229 |
| 37 | 2-trifluoromethylphenyl | 229.20 | 229 |
| 38 | 3,4-dimethoxyphenyl | 221.26 | 221 |
| 39 | 3-cyclopentoxy-4-methoxyphenyl | 275.35 | 275 |

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CLAIMS

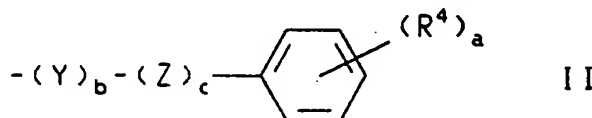
1. A compound of the formula



10

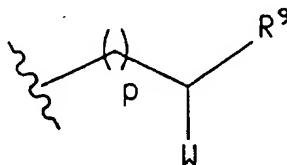
and pharmaceutically acceptable salts thereof; wherein R¹ is hydrogen, (C¹-C³)alkyl, (C²-C³)alkenyl, (C³-C⁵)cycloalkyl or methylene (C³-C⁵)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C¹-C²)alkyl or trifluoromethyl groups or up to three halogens; X is oxygen or two hydrogen atoms; R² and R³ are each independently selected from the group consisting of hydrogen, (C¹-C¹⁴)alkyl, (C¹-C¹⁴)alkoxy, (C²-C⁷)alkenyl, (C⁴-C⁷)heterocyclic group containing oxygen, sulphur, SO₂, or NR⁵ wherein R⁵ is hydrogen or (C¹-C⁴)alkyl, or a group of the formula

20



wherein a is an integer from 1 to 5; b and c is 0 or 1; R⁴ is hydrogen, hydroxy, (C¹-C⁵)alkyl, (C²-C⁵)alkenyl, (C¹-C⁵)alkoxy, (C³-C⁶)cycloalkoxy, halogen, trifluoromethyl, CO₂R⁶, CONR⁶R⁷, NR⁶R⁷, NO₂, or SO₂NR⁶R⁷ wherein R⁶ and R⁷ are each independently hydrogen or (C¹-C⁴)alkyl; wherein Z is oxygen, sulphur, SO₂ or NR⁸ wherein R⁸ is hydrogen or (C¹-C⁴)alkyl; and Y is (C¹-C⁵)alkylene or (C²-C⁶)alkenyl optionally substituted with up to two (C¹-C⁷)alkyl or (C³-C⁷)cycloalkyl groups; or a group of the formula

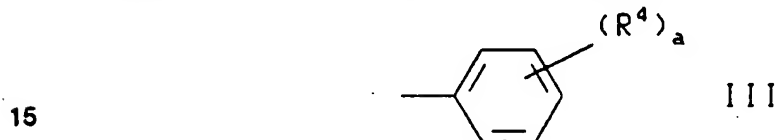
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wherein p is an integer from 1 to 3, W is oxo or hydroxy, R⁹ is (C¹-C³)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C¹-C²)alkyl, trifluoromethyl or halogen with the proviso that when R¹ is ethyl and R² is 4-methylphenyl, R³ cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R² is 4-methylphenyl and R³ is 4-fluorophenyl, R¹ cannot be phenyl, methyl or n-propyl and with the proviso that when R¹ is ethyl and R² is phenyl, R³ cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl and with the proviso that when R¹ is ethyl and R² is 4-methoxyphenyl, R³ cannot be 4-fluorophenyl.

- 10 2. A compound according to claim 1 wherein R¹ is (C¹-C³)alkyl and R² and R³ are each independently selected from the group consisting of (C³-C⁷)cycloalkyl, (C⁴-C⁷)heterocyclic group containing SO₂ or a group of the formula



wherein a is an integer from 1 to 5 and R⁴ is hydrogen, hydroxy, (C¹-C⁵)alkyl, (C¹-C⁵)alkoxy or halogen.

3. A compound according to claim 1 wherein R¹ is ethyl or isopropyl; R² is phenyl, 2-methylphenyl, 3-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl or 3-trifluoromethylphenyl and R³ is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

4. A compound according to claim 1 selected from the group consisting of:
3-ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-
25 [3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-
[3,4-c]pyridine;

3-ethyl-1-(3,4-dichlorophenyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

- 30 3-ethyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(4-fluorophenyl)-6-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

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3-ethyl-1-cyclopentyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

5 3-ethyl-1-cyclohexyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-isopropyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

10 3-ethyl-1-cyclobutyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

15 3-ethyl-1-(3-sulfolanyl)-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

20 3-ethyl-1-(3-sulfolanyl)-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

25 3-ethyl-1-cyclobutyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine.

5. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

30 6. A method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to claim 1.

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7. A pharmaceutical composition for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound
5 according to claim 1 and a pharmaceutically acceptable carrier.

8. A method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising administering to a patient
10 an effective amount of a compound according to claim 1.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | EP,A,0 531 901 (FUJISAWA) 17 March 1993 see claims 1,9 --- | 1,5 |
| X | FR,A,1 463 883 (CIBA) 30 December 1966 see example 3 --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 86, no. 5, 1977, Columbus, Ohio, US; abstract no. 29733c, T. KAMETANI ET AL. 'Studies on the syntheses of heterocyclic compounds. DCLXIII. The reaction of pyridone derivatives with diazoalkane' page 362 ; see compound III & CHEM. PHARM. BULL. 1976, 24(8), 1870 - 8 ----- | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

24 August 1994

Date of mailing of the international search report

- 5. 09. 94

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Authorized officer

Alfaro Faus, I

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